Topical Review

Efferent-mediated control of basilar membrane motion

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Medial olivocochlear efferent (MOCE) neurones innervate the outer hair cells (OHCs) of the mammalian cochlea, and convey signals that are capable of controlling the sensitivity of the peripheral auditory system in a frequency-specific manner. Recent methodological developments have allowed the effects of the MOCE system to be observed *in vivo* at the level of the basilar membrane (BM). These observations have confirmed earlier theories that at least some of the MOCE's effects are mediated via the cochlea's mechanics, with the OHCs acting as the mechanical effectors. However, the new observations have also provided some unexpected twists: apparently, the MOCEs can enhance the BM's responses to some sounds while inhibiting its responses to others, and they can alter the BM's response to a single sound using at least two separate mechanisms. Such observations put new constraints on the way in which the cochlea's mechanics, and the OHCs in particular, are thought to operate.

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Olivocochlear efferent neurones permit the central nervous system to control the way that sounds are processed in the auditory periphery, offering the potential to improve the detection of signals in background noise, to selectively attend to particular signals, and to protect the periphery from damage caused by overly loud sounds (see Guinan, 1996 for review). In mammals, the efferent neurones can be classified into two anatomically and functionally distinct groups (Warr & Guinan, 1979; Warr, 1992): lateral olivocochlear efferents originate in the lateral regions of the superior olivary complex and project thin, unmyelinated axons that terminate on the dendrites of primary afferent fibres beneath the cochlea's inner hair cells (IHCs), while medial olivocochlear efferents (MOCEs) originate in the more medial and rostral regions of the superior olivary complex and project thicker, myelinated axons that terminate directly on the outer hair cells (OHCs) of the organ of Corti (see Fig. 1). The lateral efferents are capable of producing increases and decreases in the activity of the cochlea's primary afferents (the type-I auditory nerve fibres, or ANFs) that last for many minutes, but they have no known effects on the cochlea's mechanics (Groff & Liberman, 2003). In contrast, the MOCEs can change the sensitivity of the cochlea over much shorter time scales (with time constants of tens of milliseconds and tens of seconds for 'fast' and 'slow' effects, respectively; see Sridhar *et al*. 1995), and they have notable effects on the cochlea's mechanics (Mountain, 1980; Siegel & Kim, 1982) as well as on ANF responses to sound (Wiederhold & Kiang, 1970). Since MOCEs do not terminate directly onto the type-I ANFs (which innervate only IHCs), MOCE effects on the auditory nerve must be mediated indirectly, and the most likely way for this to happen is via changes in the cochlea's mechanics. It is commonly hypothesized (i) that MOCEs inhibit the mechanical amplification of low-level sounds that occurs before the sound stimulates the IHCs and ANFs (for review, see Guinan, 1996), and (ii) that the mechanical amplification is produced by OHC electromotility (Brownell *et al*. 1985; Ashmore, 1987), which boosts the vibratory responses of the basilar membrane (BM) via a positive feedback loop (for reviews, see Dallos, 1992; Fettiplace & Hackney, 2006). Technological advances made over the past two decades, including the application of laser interferometry to *in vivo* studies of BM motion, have permitted these two hypotheses to be tested directly. The present article will review the findings from several recent studies that have observed the mechanical effects of the MOCE system on BM motion.

MOCE activity inhibits BM motion evoked by characteristic frequency tones

The most fundamental finding of all studies performed to date is that MOCE activity reduces the motion of the BM that is evoked by characteristic frequency (CF)

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tones, as illustrated in Fig. 2 (Murugasu & Russell, 1996; Russell & Murugasu, 1996, 1997; Dolan *et al.* 1997; Cooper & Guinan, 2003, 2006; Guinan & Cooper, 2003). Most investigations have found that the mechanical inhibition is strongest for tones presented at low-to-moderate sound levels, with effects that become progressively smaller or even negligible at higher sound levels. These findings are entirely consistent with the idea that MOCEs work by reducing the gain of the cochlear amplifier (i.e. of the OHC-BM feedback loop described above). According to this idea, the MOCE effects are strongest at low sound levels because the OHC–BM feedback loop amplifies low level sounds more than high level sounds (the efficiency of the feedback loop is thought to decrease with increasing intensity because mechano-electrical transduction in OHCs saturates for high level tones – see Zwicker, 1979; Patuzzi *et al.* 1989). Similarly, the MOCE effects are strongest at the CF because this is where the OHC–BM feedback loop works best (the principal effect of the feedback loop is to counteract the mechanical damping of the cochlear partition, and altering the damping of a resonant system produces its largest effects at, or near, the CF – e.g. see de Boer & Nuttall, 2000).

There is only one exception to the finding that MOCE effects on BM motion are strongest for low-level, CF sounds: Russell & Murugasu (1997) reported that MOCE effects were largest for CF tones of around 50–75 dB SPL and remained significant even at the highest levels tested (i.e. 85–100 dB SPL). While this finding is not consistent with the simple, intensity-dependent, gain-reduction hypothesis described above, it ties in well with observations that were made in single ANFs just one year earlier: Guinan & Stankovic (1996) observed that MOCE-evoked 'level shifts' in low- and medium-spontaneous rate ANFs were largest in the 50–75 dB SPL range, and remained substantial even at 100 dB SPL. Guinan & Stankovic (1996) suggested that these findings could be explained by a combination of MOCE effects: a mechanical effect on the cochlear amplifier (as described above), and an electrical effect on the IHCs and/or ANFs that is mediated by MOCE-evoked decreases in the endocochlear potential (Fex, 1967; Geisler, 1974; Guinan, 1996). It is unlikely that this electrical effect would have a strong mechanical correlate at the level of the BM, however, and it is unlikely that it would operate *only* for CF tones (as observed by Russell & Murugasu, 1997), so the electrical effect cannot be used to reconcile the findings of Russell & Murugasu (1997) with those of others. Another potential explanation is that the effects noted by Russell & Murugasu (1997) were caused by a fortuitous combination of MOCE fast and slow effects: these effects were only discovered in 1995 (see Sridhar *et al.* 1995), and no attempts to separate them were made in the earliest mechanical studies.

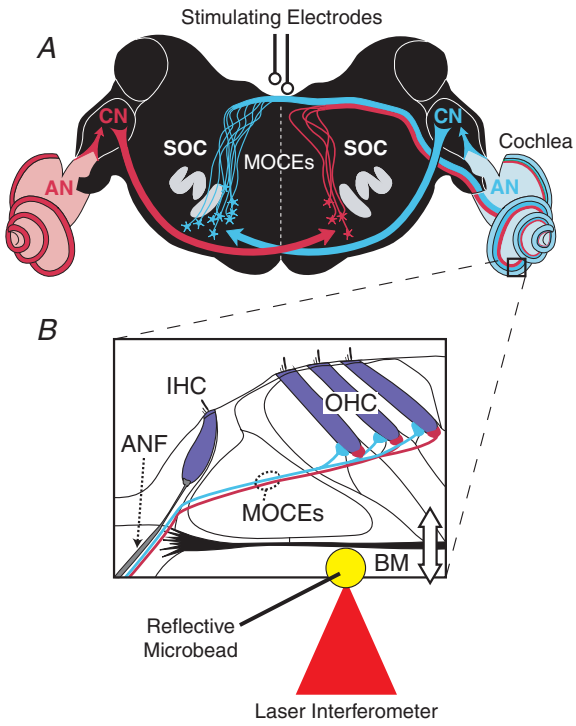

Figure 1. Simplified circuitry, and experimental approaches to the medial olivocochlear efferent system
A, schematic section of the mammalian brainstem illustrating bilateral origins of MOCE neurones in the medial regions of the superior olivary complex. Electrical stimulation of the MOCE system is facilitated by exposing the floor of the fourth ventricle at the midline, where both uncrossed (red) and crossed (cyan) MOCE fibres lie close to the surface of the brainstem. *B*, schematic section of organ of Corti illustrating MOCE innervation of the outer hair cells. Interferometric recording of sound-evoked motion (white arrows) is facilitated by placing reflective microbeads on the undersurface of the basilar membrane. Illustrations based on originals provided by M. C. Liberman. Abbreviations: AN – auditory nerve; ANF – auditory nerve fibre; BM – basilar membrane; CN – cochlear nucleus; IHC – inner hair cell; OHC – outer hair cell; MOCE – medial olivocochlear efferent; SOC – superior olivary complex.

MOCE effects that vary unexpectedly with sound frequency

The idea that inhibition of the cochlear amplifier is the only mechanical effect evoked by MOCE activity has been challenged by two observations at the level of the BM. Firstly, Russell & Murugasu (1998) reported MOCE-evoked inhibition of BM motion well below CF, as well as at CF. Russell & Murugasu's single observation of below-CF inhibition is potentially highly important, because if true, it would demonstrate that OHCs can affect BM motion even in regions where the cochlea's mechanical impedance is dominated by the stiffness (as opposed to the damping) of the BM (see Allen, 1990; Kolston *et al.* 1990). MOCE inhibition of below-CF BM motion might also explain the more extensive observations of below-CF inhibition that have been made at the level of

individual ANFs by Stankovic & Guinan (1999). For the time-being, however, Russell & Murugasu's observation of below-CF inhibition on the BM remains unique, and is countered by the negative findings of several other BM studies (e.g. Murugasu & Russell, 1996; Russell & Murugasu, 1996; Guinan & Cooper, 2003; Cooper & Guinan, 2006). A definitive resolution to the issue of MOCE effects on below-CF BM motion therefore awaits further, more systematic studies.

The second observation that does not fit with the conventional view that MOCE activity simply turns down the gain of the cochlear amplifier was reported by Dolan *et al.* (1997), who found that BM responses to some tones were enhanced by MOCE activation, while those to others were inhibited. Dolan *et al.* (1997) observed enhanced BM motion only for tones that were well above neural thresholds (i.e. moderate and high level tones) and well above the BM's CF, and their findings have now been replicated by two other groups (Russell & Murugasu, 1998; Guinan & Cooper, 2003; Cooper & Guinan, 2006). One example of this phenomenon is shown in Fig. 2*A*, where the 20 kHz data show MOCE-inhibited BM motion at low sound pressure levels, and MOCE-enhanced BM motion at high levels. The only hypothesis that has been put forward to explain how the MOCEs might enhance BM motion posits that BM motion can be driven in at least two ways: one way which is inhibited strongly by the MOCE system (producing an 'inhibitable' motion component), and one way which is not inhibited so strongly (producing an essentially 'un-inhibitable' component) (Guinan & Cooper, 2003). According to this hypothesis, MOCE-enhanced BM motion results when the 'inhibitable' and the 'un-inhibitable' components are comparable in size and occur in antiphase to one another, such that they interfere destructively on the BM. MOCE-evoked inhibition (of the 'inhibitable' component) would then reduce the amount of destructive interference that occurs, and increase the overall amplitude of the BM's motion. The fact that MOCE-evoked increases in BM motion are accompanied by phase shifts of up to 180 deg (Guinan & Cooper, 2003) lends support to this hypothesis. However, there is no evidence (to date) of similar MOCE-evoked response enhancements at subsequent stages of the auditory periphery (e.g. in the IHCs or ANFs; see Brown & Nuttall, 1984; Guinan & Gifford, 1988), and it is not clear either (i) how each type of BM motion might translate into IHC (or ANF) activity or (ii) what the functional significance of the MOCE-enhanced BM motion might be. As most previous IHC and ANF studies have focused on the MOCE effects seen at (or near) neural thresholds, or only at CF for supra-threshold levels, it remains possible that future studies could reveal clear counterparts of the enhanced BM motion, as noted by Dolan *et al.* (1997).

MOCE activity can alter BM motion using two separate mechanisms

Another unexpected finding resulted from recent attempts to find mechanical counterparts to the 'fast' and 'slow' forms of MOCE-evoked inhibition that had been observed in studies of the auditory nerve (see Sridhar *et al.* 1995; Sridhar *et al.* 1997). While Cooper & Guinan (2003, 2006) observed that BM motion could be inhibited on both fast and slow time scales by MOCE stimulation (as shown in Fig. 3), they also found that the two forms of inhibition resulted in oppositely directed changes in the BM's response phase at CF (as illustrated in Fig. 3*B*). The fast inhibition caused the BM to respond to CF tones slightly earlier in time than normal (on a cycle-by-cycle

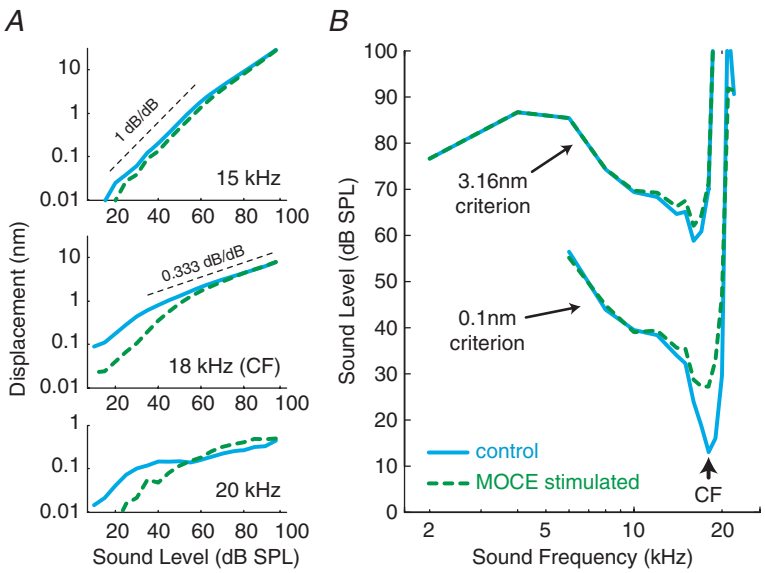

Figure 2. Frequency dependence of MOCE fast effects on BM motion in the guinea-pig cochlea
A, amplitude growth functions for BM responses to tones below, near, and above the BM's characteristic frequency (CF) immediately before (blue) and during (green) electrical stimulation of MOCE fibres. *B*, iso-displacement tuning curves for BM motion immediately before (blue) and during (green) MOCE stimulation. The two iso-displacement criteria (0.1 and 3.16 nm) were selected to contrast the relative strengths of the MOCE effects at sound levels near and well-above the thresholds of most auditory nerve fibres, respectively. Adapted with permission from Cooper & Guinan (2006).

basis – this is reflected by the phase leads shown in Fig. 3*B*), while the slow inhibition caused the BM to respond slightly later than normal (reflected by the phase lags in Fig. 3*B*). These observations rule out the possibility that the fast and slow effects are caused by similar functional changes in individual OHCs (such as electrical conductance changes that occur on different time scales, as proposed by Sridhar *et al.* 1995). However, Cooper & Guinan's (2003, 2006) findings are compatible with suggestions that the OHCs can influence BM motion in multiple ways (see Allen, 1990; Kolston *et al.* 1990). This suggestion is further supported by studies into the effects of acetylcholine (ACh, the MOCE's principal neurotransmitter) on isolated OHCs: these studies imply that the slow form of inhibition is likely to reflect changes in the axial stiffness of the OHCs (Dallos *et al.* 1997; He *et al.* 2003), while the fast form is likely to reflect decreases in OHC electromotility *per se*. One way to test this possibility might be to investigate the frequency dependence of the fast and slow effects on the BM in more detail, although preliminary evidence suggests that neither form of inhibition causes a large change in the BM's CF (see Cooper & Guinan, 2003, 2006).

The explanation for the origin of two separate MOCE effects may lie in the OHC's unusual postsynaptic apparatus, which is more complicated than that at a typical synapse. The ACh released by MOCE terminals acts on $\alpha 9/\alpha 10$ ACh receptors (Elgoyhen *et al.* 1994, 2001), and opens non-specific cation channels that allow calcium entry into the OHCs. This calcium then opens calcium-activated potassium (SK) channels, causing the cells to become hyperpolarized (Housley & Ashmore, 1991; Fuchs, 1992; Blanchet *et al.* 1996; Evans, 1996; Oliver *et al.* 2000). In addition, calcium-activated release of calcium from intracellular stores (such as the extensive synaptic and subsurface cisterns of the OHCs) may lead to calcium sparks (Sridhar *et al.* 1997), producing further conductance changes as well as changes (e.g. by protein phosporylation – see Kalinec *et al.* 2000) in both the OHC's cytoskeleton and the motor proteins of the OHC plasma membrane (He *et al.* 2003).

Regardless of the exact origins of the fast and slow effects within the OHCs, the implication of the BM studies described above is that OHCs use *at least* two different effector mechanisms to influence the processing of sound by the BM. The functional consequences of these mechanisms remain subject to much speculation. MOCE slow effects may play a role in protecting the auditory system from the damaging effects of acoustic over-stimulation (Reiter & Liberman, 1995), for example, and MOCE fast effects are thought to facilitate the detection and/or discrimination of signals in the presence of background noise (Winslow & Sachs, 1987; for review see Guinan, 1996). However, preliminary investigations at the level of the BM (e.g. Cooper & Guinan, 2003, 2006) suggest that the two forms of inhibition are fairly similar in their dependencies on the frequency

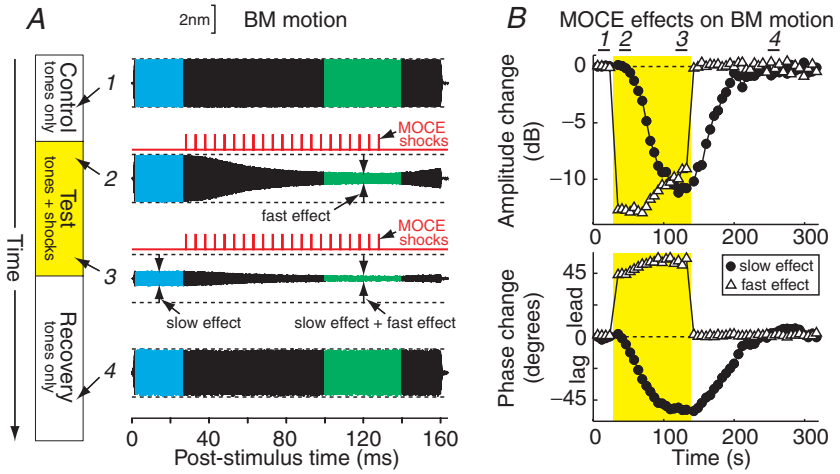

Figure 3. Fast and slow effects of MOCE stimulation on BM motion in the guinea-pig cochlea
A, BM responses to 160 ms tone-bursts at four instants before, during and after a 100 s period of repetitive MOCE stimulation (the yellow 'test' period). The tone bursts were presented at 35dB SPL at the BM's CF (19 kHz), and the stimulus repetition period was 330 ms. Pulse trains (red) above responses 2 and 3 illustrate the fine timing patterns of the MOCE stimulation. Slow effects of the MOCE stimulation are manifest as changes in the BM responses near the onset of each tone (shaded blue) *across* individual tone-bursts (i.e. as differences from the control or baseline responses, illustrated by horizontal dashed lines). Fast effects are manifest as changes in the BM responses *within* individual tone-bursts (i.e. as differences between the blue and green sections of each response). *B*, amplitude and phase changes attributed to the fast (△) and slow (●) effects. Each effect inhibits the BM's motion by more than 10 dB, but the fast and slow forms of inhibition are accompanied by phase leads and phase lags, respectively. Reproduced from Cooper & Guinan (2003).

and intensity of acoustic stimulation. Whether or not the multiple mechanisms are actually used separately, for different purposes or under different conditions, or whether they merely provide the auditory system with parallel mechanisms to achieve similar ends, remains to be seen.

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